AMENDMENTS TO THE SPECIFICATION

(Note: Bracketing Of References As In Original Specification, Do Not Delete)

Page 15 Para 2

The modified cells which collectively harbor an allelic series of modifications in substantially every gene are particularly useful in investigating diseases which are associated with more than one modification in a given gene. Several such diseases are known in the art including, for example, epithelial ovarian cancer, sporadic breast cancer, familial breast cancer, cystic fibrosis, and autosomal dominant polycystic kidney disease. For example, epithelial ovarian cancer has been associated with 45 mutations in exons 5-8 of the p53 gene. Overall, 72% of the mutations were transitions, 24% were transversions, and 4% were microdeletions. Allelic deletion of the other p53 allele was seen in 67% of ovarian cancers in which a p53 mutation was present [Kohler *et al.* (1993) J. Natl. Cancer Inst. 85(18):1513-1519]. Similarly, familial breast cancer has also been shown to be associated with over 200 distinct mutations in the BRCA1 gene, including missense and protein-truncating mutations [Greenman *et al.* (1998) 21(3):244-249]. Cystic fibrosis was found to be associated with over 550 mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene [see, *e.g.*, [Zielenski and Tsui (1995) Ann. Rev. Genetics 29:777-807; Dean and Santis (1994) Hum. Genet. 93(4):364-368]. A list of the mutations associated with cystic fibrosis is available at ~~[[http://]]~~www.genet.sickkids.on.ca/cftr. Another disease associated with several mutations in a given gene is autosomal dominant polycystic kidney disease (ADPKD) in which phenotypically indistinguishable traits are caused by mutations in at least three distinct autosomal genes, *i.e.*, PKD1, PKD2 and PKD3 [Sessa *et al.* (1997) J. Nephrol. 10(6):295-310; Watnick *et al.* (1997) Hum. Molec. Genetics 6:1473-1481; Veldhuisen *et al.* (1997) 61:547-555].

Page 22 Para 2

The methods of the invention are contemplated to include within their scope any agent which is capable of introducing a modification into the genome of a cell. These agents are exemplified by chemicals and electromagnetic radiation. Exemplary chemicals are described at ~~[[http://]]~~dir.niehs.nih.gov/dirtb/dirrtg/chemicalsstudiedindex2.htm including, but not limited to, *N*-ethyl-*N*-nitrosurea (ENU), methylnitrosourea (MNU), procarbazine hydrochloride (PRC), triethylene melamine (TEM), acrylamide monomer (AA), chlorambucil (CHL), melphalan (MLP), cyclophosphamide (CPP), diethyl sulfate (DES), ethyl methane sulfonate (EMS), methyl methanes ulfonate (MMS), 6-mercaptopurine (6MP), mitomycin-C (MMC), procarbazine (PRC), *N*-methyl-*N'*-nitro-*N*-nitrosoguanidine (MNNG), ^3H_2O, and urethane (UR) [see, *e.g.*, Russell *et al.*, Factors affecting the nature of induced mutations, In "Biology of Mammalian Germ Cell Mutagenesis," Banbury Report 34, Cold Spring Harbor Laboratory Press (1990), pp. 271-289; Rinchik (1991) Trends in Genetics 7(1); Marker *et al.* (1997) Genetics 145:435-443]. Electromagnetic radiation is exemplified by ultraviolet light, X-ray radiation, gamma-radiation, *etc.*